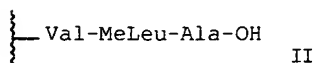
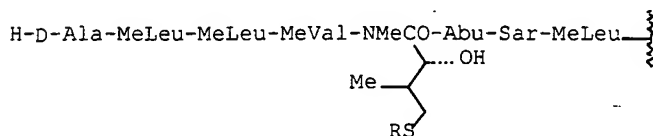
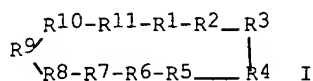


L35 ANSWER 232 OF 272 HCAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1989:497726 HCAPLUS Full-text
 DOCUMENT NUMBER: 111:97726
 TITLE: New cyclosporin analogs with modified C-9-amino acids
 as immunosuppressants
 INVENTOR(S): Witzel, Bruce W.
 PATENT ASSIGNEE(S): Merck and Co., Inc., USA
 SOURCE: Brit. UK Pat. Appl., 59 pp.
 CODEN: BAXXDU
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
GB 2205317	A1	19881207	GB 1988-12273	19880524
US 4798823	A	19890117	US 1987-57196	19870603
US 4885276	A	19891205	US 1988-261868	19881024
PRIORITY APPLN. INFO.:			US 1987-57196	A 19870603
OTHER SOURCE(S):		CASREACT 111:97726; MARPAT 111:97726		

GI



AB The title peptides [I; R₁ = NR₁₂CH[CH(OH)CHR₁₃CH₂XR]CO (Q), (4R)-4-[(E)-2-butenyl]-4-methyl-N-methyl-L-threonine residue; R = H, lower (halo)alkyl, lower alkenyl, (un)substituted aryl or heteroaryl, etc.; R₁₂ = lower alkyl, lower alkylphenyl, aryl; R₁₃ = lower alkyl; X = S, SO, SO₂, O, MeLeuN; R₂ = L-NHCHPrCO (Abu), Nva, Thr, R₁; R₃ = MeGly, NMeCH(SMe)CO, D-MeAla, MeAla, D-Pro; R₄ = MeLeu; R₅ = Val, Nval; R₆ = MeLeu; R₇ = Ala, Abu, Phe; R₈ = D-Ala, Ala; R₉ = MeLeu, MeVal; R₁₀ = MeLeu, Leu; R₁₁ = MeVal, Val, MeLeu, Abu] useful as immunosuppressants, were prepared by cyclization of linear undecapeptides (II). Reaction of (2R,3R)-3,4-isopropylidene-2-methyl-1-O-p-toluenesulfonyl-1,2,4- butanetriol with MeSNa in MeOH followed successively by deacetonation and selective benzylation with BzCl gave (2R,3R)-MeSCH₂CHMeCH(OH)CH₂OBz which was etherified with EtOCH:CH₂ in CH₂Cl₂ containing CF₃CO₂H and the resulting ether was saponified to give (2R,3R)-MeSCH₂CHMeCH(OCHMeOEt)CH₂OH. Oxidation of the

latter with SO₂-pyridine complex and Me₂SO containing Et₃N followed by hydrolysis gave (2R,3R)-MeSCH₂CHMeCH(OH)CHO which underwent addition reaction with KCN and MeNH₂.HCl in MeOH to give (2RS,3R,4R)- MeSCH₂CHMeCH(OH)CH(CN)NHMe. Cyclocondensation of the latter with 1,1'-carbonyldiimidazole in CH₂Cl₂ gave 3-methyl-5-[1-methyl-2-(methylthio)ethyl]-2-oxooxazolidine-4-carbonitrile which was converted into Et oxooxazolidine-4-carboxylate derivative via Et oxooxazolidine-4- imidate. Hydrolysis of the carboxylate followed by saponification gave (2S,3R,4R)- MeSCH₂CHMeCH(OH)CH(NHMe)CO₂H (III). II (R = Me) was prepared by block synthesis of 1N,3O-isopropylidene derivative of III with 2 protected peptide fragments followed by deprotection and then cyclized to give I [R₁=(2S,3R,4R)-NHMeCH[CH(OH)CHMeCH₂SMe]CO; R₂ = Abu, R₃ = MeGly, R₄ = R₆ = R₉ = R₁₀ = MeLeu; R₅ = Val, R₇ = Ala, R₈ = D-Ala, R₁₁ = MeVal]. In R. Handschumacher's cyclophilin binding assay, the latter showed 179% of cyclosporin A activity.

IT 122008-24-6P 122008-25-7P 122008-26-8P
 122008-27-9P 122008-28-0P 122008-29-1P
 122008-30-4P 122008-31-5P 122008-32-6P
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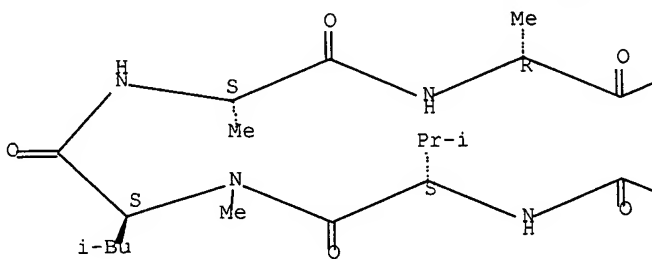
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (preparation of, as immunosuppressant)

RN 122008-24-6 HCAPLUS

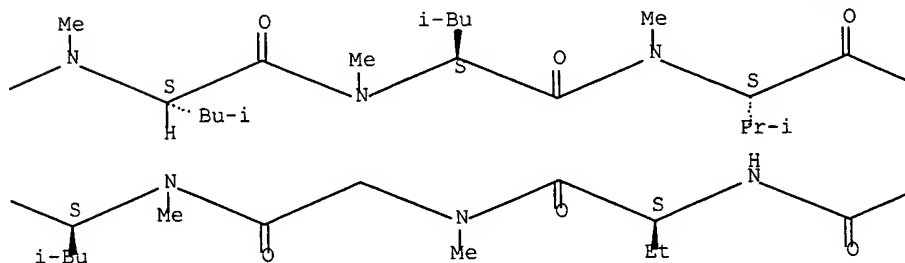
CN Cyclosporin A, 6-[(3R,4R)-3-hydroxy-N-methyl-5-(methylthio)-L-leucine]-
 (9CI) (CA INDEX NAME)

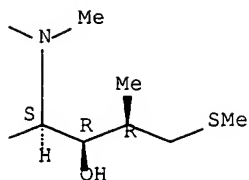
Absolute stereochemistry.

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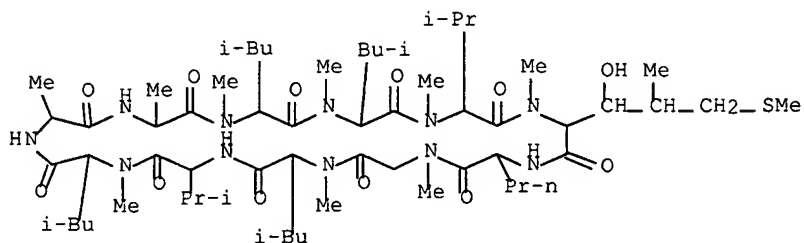
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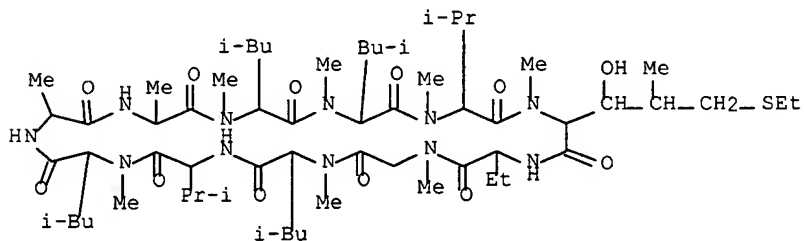
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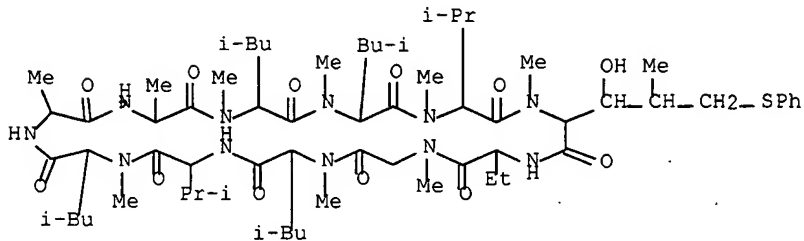
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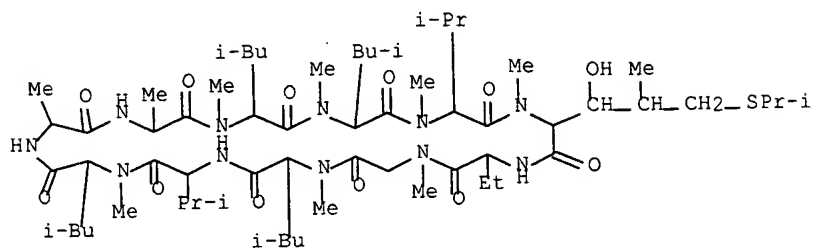


RN 122008-27-9 HCAPLUS

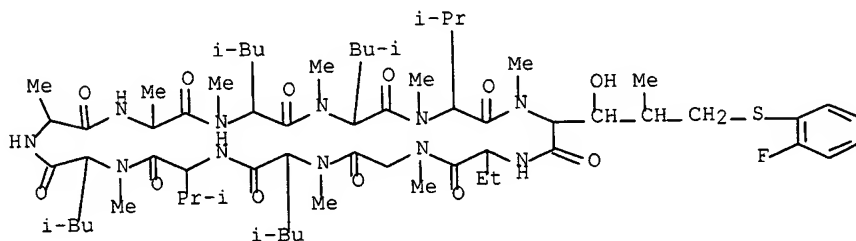
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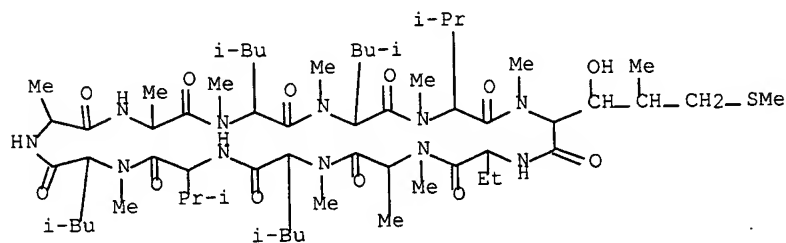
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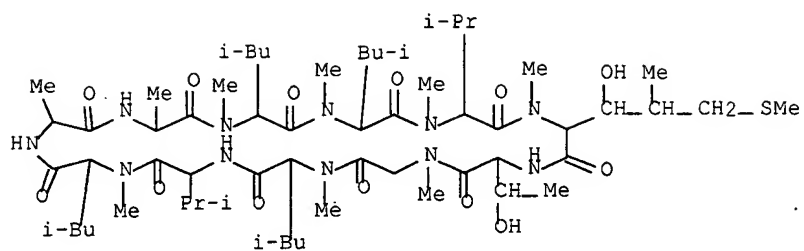
RN 122008-29-1 HCAPLUS
 CN Cyclosporin A, 6-[(3R,4R)-5-[(2-fluorophenyl)thio]-3-hydroxy-N-methyl-L-leucine]- (9CI) (CA INDEX NAME)



RN 122008-30-4 HCAPLUS
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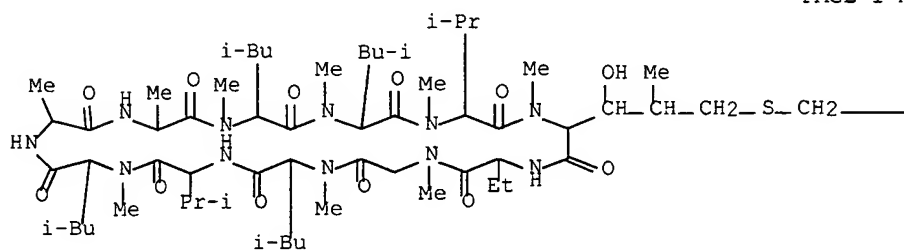


RN 122008-31-5 HCAPLUS
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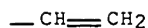


RN 122008-32-6 HCAPLUS
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 (9CI) (CA INDEX NAME)

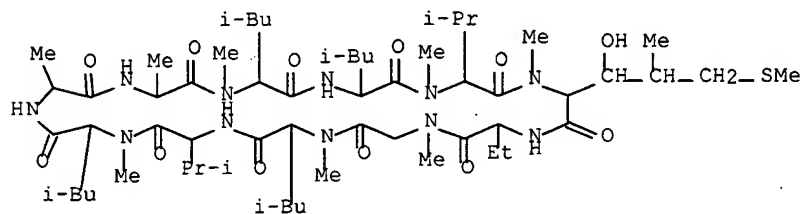
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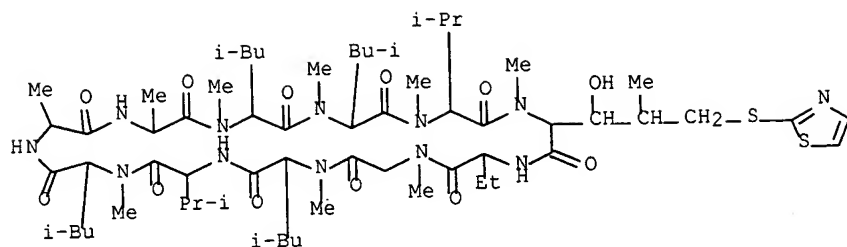
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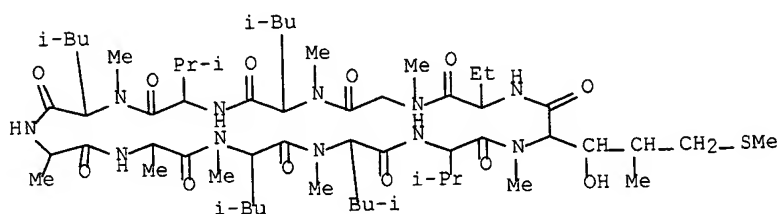
RN 122008-33-7 HCAPLUS
 CN Cyclosporin A, 4-L-leucine-6-[(3R,4R)-3-hydroxy-N-methyl-5-(methylthio)-L-leucine]- (9CI) (CA INDEX NAME)



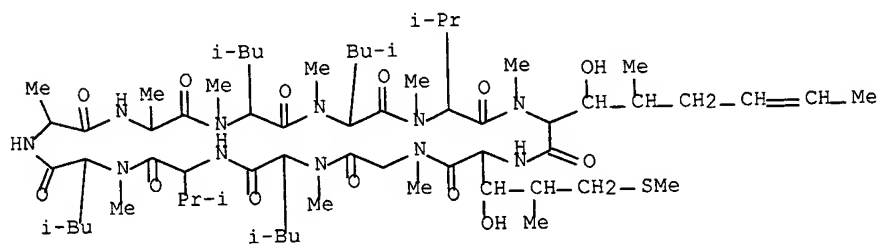
RN 122008-34-8 HCAPLUS
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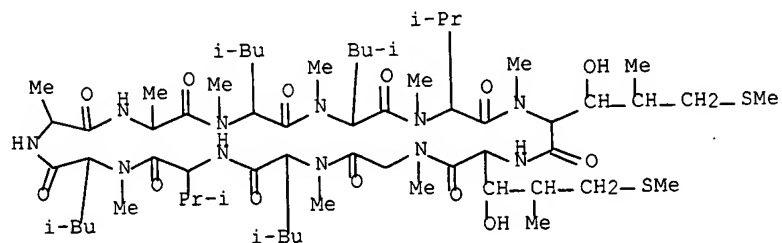
RN 122008-35-9 HCAPLUS
 CN Cyclosporin A, 5-L-valine-6-[(3R,4R)-3-hydroxy-N-methyl-5-(methylthio)-L-leucine]- (9CI) (CA INDEX NAME)



RN 122008-37-1 HCAPLUS
 CN Cyclosporin A, 2-L-alanine-7-[(3R,4R)-3-hydroxy-5-(methylthio)-L-leucine]- (9CI) (CA INDEX NAME)

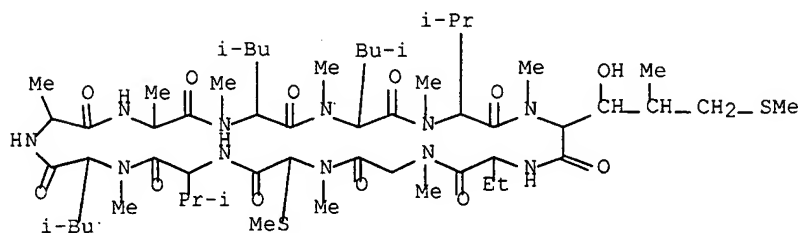


RN 122008-38-2 HCAPLUS
 CN Cyclosporin A, 6-[(3R,4R)-3-hydroxy-N-methyl-5-(methylthio)-L-leucine]-7-[(3R,4R)-3-hydroxy-5-(methylthio)-L-leucine]- (9CI) (CA INDEX NAME)



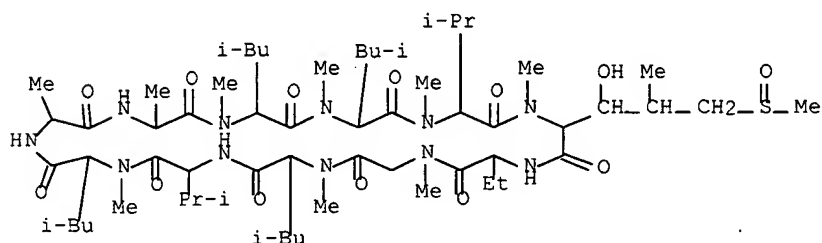
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CN Cyclosporin A, 6-[(3R,4R)-3-hydroxy-N-methyl-5-(methylthio)-L-leucine]-9-[N-methyl-L-2-(methylthio)glycine]- (9CI) (CA INDEX NAME)



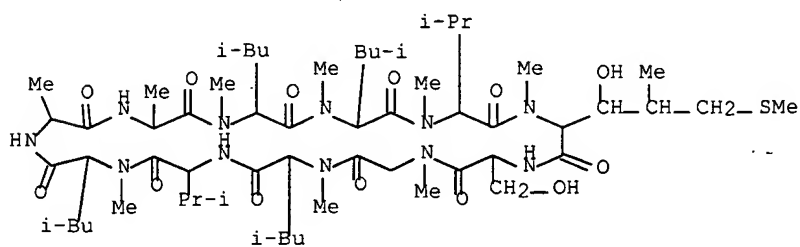
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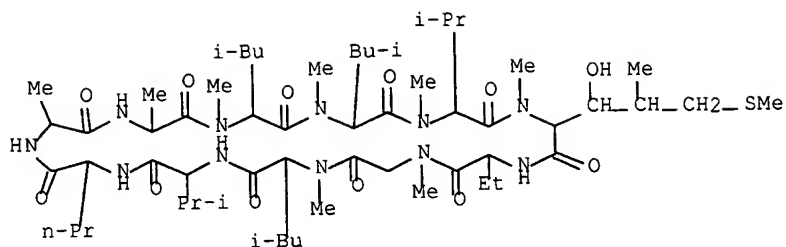
RN 122008-41-7 HCAPLUS

CN Cyclosporin A, 6-[(3R,4R)-3-hydroxy-N-methyl-5-(methylthio)-L-leucine]-7-L-serine- (9CI) (CA INDEX NAME)



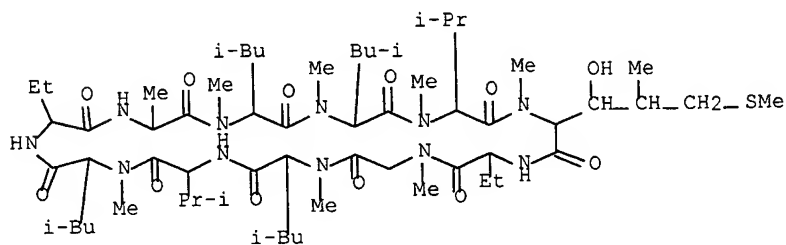
RN 122023-77-2 HCAPLUS

CN Cyclosporin A, 6-[(3R,4R)-3-hydroxy-N-methyl-5-(methylthio)-L-leucine]-11-L-norvaline- (9CI) (CA INDEX NAME)



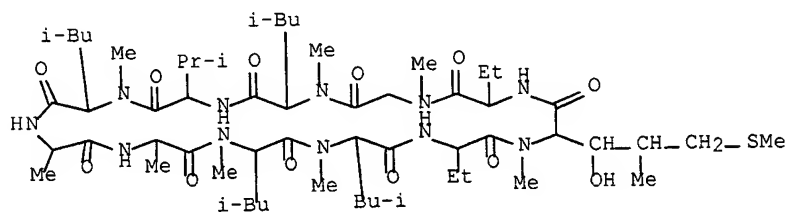
RN 122023-78-3 HCAPLUS

CN Cyclosporin A, 1-(L-2-aminobutanoic acid)-6-[(3R,4R)-3-hydroxy-N-methyl-5-(methylthio)-L-leucine]- (9CI) (CA INDEX NAME)



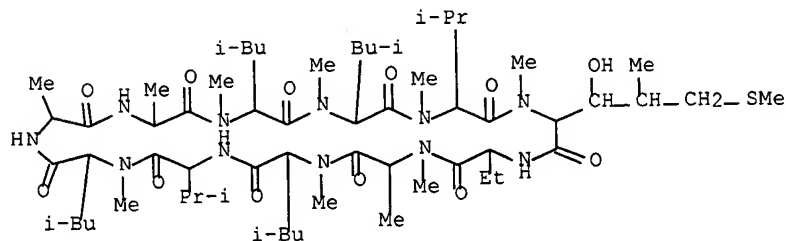
RN 122023-79-4 HCAPLUS

CN Cyclosporin A, 5-(L-2-aminobutanoic acid)-6-[(3R,4R)-3-hydroxy-N-methyl-5-(methylthio)-L-leucine]- (9CI) (CA INDEX NAME)



RN 122088-55-5 HCAPLUS

CN Cyclosporin A, 6-[(3R,4R)-3-hydroxy-N-methyl-5-(methylthio)-L-leucine]-8-(N-methyl-L-alanine)- (9CI) (CA INDEX NAME)

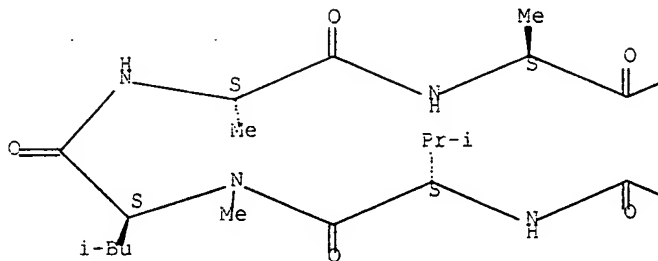


RN 122088-56-6 HCAPLUS

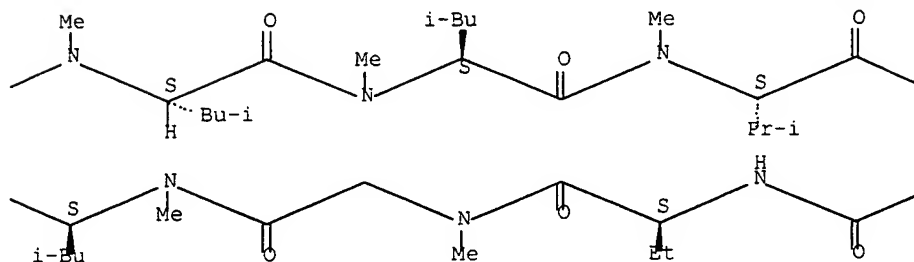
CN Cyclosporin A, 2-L-alanine-6-[(3R,4R)-3-hydroxy-N-methyl-5-(methylthio)-L-leucine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

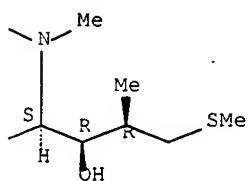
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